REMARKS

After entry of this amendment, claims 1, 3-20, and 22-34 are pending. Claims 1, 20, 33 and 34 are amended to expedite prosecution and claim 13 is amended to correct a typographical error.

35 U.S.C. § 112 Rejections

Reconsideration is respectfully requested of the rejection of claims 1-34 as failing to satisfy the enablement requirement of 35 U.S.C. § 112. As explained in the prior response, applicant respectfully maintains that the pending claims are fully enabled. However, to expedite prosecution, the claims have been amended to recite methods for reducing mucositis in patients exposed to radiation or anti-tumor platinum-coordination compounds. In addition, Applicant provides a declaration of Dr. Prasad Sunkara[1] presenting data generally showing the reduction of the incidence and severity of oral mucositis in human patients that have head and neck cancers that are treated with either radiation alone or radiation combined with cisplatin. The oral formulation used in the Phase 1 study included D-methionine as the only active ingredient; non-active formulation ingredients included methylparaben, propylparaben, xantan gum, polysorbate 80, sorbitol, chewing gum, and purified water. This formulation is described in more detail in Table 1 of U.S. Patent Application Publication No. 2006/0058390, which is attached hereto. Therefore, the amended claims satisfy the enablement requirement of 35 U.S.C. § 112.

Moreover, claims 4, 5, and 6 recite D-methionine, L-methionine, or DL-methionine as the protective agent. Therefore, even if, for argument's sake, claims 1, 3, 7-20, and 22-34 were deemed not to be enabled, claims 4, 5, and 6 are nonetheless enabled because the experimentation required to test for each agent's protectant efficacy against mucositis is narrowly limited, and certainly not undue. Further, claims 3 and 22 recite L-methionine, a mixture of D-methionine and L-methionine, normethionine, homomethionine, methioninol, hydroxy methionine, or ethionine as the

[1] Dr. Sunkara is the CEO of Molecular Therapeutics; Molecular Therapeutics is a licensee of the instant application.

protective agent and claims 33 and 34 recite S-adenosyl-L-methionine as the protective agent. Similar to claims 4, 5, and 6, these claims are enabled because the experimentation required to test for each agent's protectant efficacy against mucositis is also narrowly limited, and not undue. Thus, claims 3, 4, 5, 6, 22, 33 and 34 satisfy the enablement requirement of 35 U.S.C. § 112.

35 U.S.C. § 103 Rejection

Reconsideration is respectfully requested of the rejection of claims 1-32 as unpatentable over U.S. Patent No. 6,265,386 (Campbell) in view of U.S. Patent No. 4,961,926 (Gabrilove). It is respectfully noted that the Campbell patent makes no mention of mucositis resulting from any type of insult; and that the patent contains not the remotest suggestion that methionine or methionine-like moieties would have any value in dealing with mucositis resulting from radiation exposure or administration of an anti-tumor platinum-coordination compound. Thus, from this disclosure alone, it would not have been obvious to a person of skill in the art that methionine would be a protectant for mucositis.

Gabrilove discloses methods of preventing mucositis comprising administering granulocyte colony stimulating factor (GCSF) or a polypeptide analog thereof. In particular, the GCSF analog may be a nonglycosylated polypeptide having an amino acid sequence identical to the sequence of the polypeptide component of naturally occurring GCSF (GCSF contains at least 144 amino acids) except for the presence of an additional methionine at the N-terminus. In one embodiment described in the Gabrilove reference, this 20,000 Dalton protein has one additional methionine residue to give a total of 145 amino acids. A person of ordinary skill would not have considered the disclosure by Gabrilove et al. of the efficacy of a specific hormone-like protein to suggest that mucositis could be effectively treated with a single monomeric amino acid. By teaching the need to administer a 20,000 Dalton hormone-like protein, Gabrilove et al. lead away from any contemplation of the effectiveness of methionine or another methionine-like small molecule alone. An examination of Campbell together with Gabrilove would not have led a person of ordinary skill to find the present claims for

reducing mucositis using the small molecule methionine (having a weight of approximately 150 Daltons) obvious without resorting to impermissible hindsight using applicant's disclosure as a template. It is respectfully submitted that the Office has failed to establish obviousness based on any reference or by evidence of the level of skill in the art or the nature of the problem that is not based upon impermissible hindsight reconstruction.

Further, applicant submits herewith an Information Disclosure Statement citing the prosecution history of related applications (U.S. Application Nos. 09/911,195, 10/694,432, 10/694,448, and 11/324,744). In addition, with respect to the statements on page 29, lines 24-34, applicant would like to clarify that testing in human or animal patients had not been done at the time of filing of the application and these statements were not meant to imply that such testing had been performed.

Applicant submits that the present application is now in a condition for allowance and requests early allowance of the pending claims.

Respectfully submitted,

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JSH/dep

TABLE 1

Ingredient	Quantity in grams/60 mL	Active/Non-Active
D-Methionine	12.000	ACTIVE
Methylparaben	0.060	NON-ACTIVE
Propylparaben	0.006	NON-ACTIVE
Xantan gum	0.072	NON-ACTIVE
Polysorbate 80 (Tween-80 ™)	0.060	NON-ACTIVE
Sorbitol	3.000	NON-ACTIVE
Chewing gum, orange, cherry, or mango flavor	0.1 mL	NON-ACTIVE
Purified water	Up to 60 mL	NON-ACTIVE

hours before, and subsequent administration is within about 4 hours after administration of the platinum-containing chemotherapeutic agent or exposure to radiation. Even more preferably, prior administration of the effective amount of methionine protective agent is within about 1 hour before, and subsequent administration is within about 1 hour after, administration of the platinum-containing chemotherapeutic agent or exposure to radiation. Still more preferably, prior administration of the effective amount of methionine protective agent is within about one-half hour before, and subsequent administration is within about one-half hour after, administration of the platinum-containing chemotherapeutic agent or exposure to radiation.

The platinum-containing chemotherapeutic agent can be administered parenterally, for example by slow intravenous infusion, or by local injection, as discussed above. The methionine protective agent can be administered as described above, preferably, orally, parenterally by intravenous injection or slow infusion, intraperitoneally or topically.

In a preferred embodiment of the present invention, when treating or preventing mucositis due to exposure to radiation, the effective amount of the protective agent can be administered prior to, simultaneously with, or subsequently to the radiation exposure. For example, it has been found that administering the protective agent to a patient from about 6 hours before the radiation exposure to about 6 hours after the radiation exposure, preferably from about 4 hours before the radiation exposure to about 4 hours after the radiation exposure, more preferably from about 2 hours before the radiation exposure to about 2 hours after the radiation exposure, and even more preferably from about 1 hour before to about 1 hour after the radiation exposure, can significantly ameliorate or prevent mucositis in a human or animal patient.